Attorney Docket 1662/63303

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Igor RUKHMAN et al.
Serial No.	:	10/802,627
Filed	:	March 17, 2004
Title	:	POLYMORPHS OF VALSARTAN
Examiner	:	Chung, Susannah Lee
Art Unit	:	1626

Declaration of Gautam R. Desiraju Under 37 CFR 1.132

I, Professor Gautam R. Desiraju, Ph.D., do hereby declare as follows:

1. I am a Professor of Chemistry at the University of Hyderabad. I have been employed as a faculty member at the University of Hyderabad since 1979, first as a lecturer in 1979, then as a Reader in 1984, and then as professor since 1990. I received a bachelor's in science degree from the University of Bombay in 1972. I received a Ph.D. in Chemistry from the University of Illinois at Urbana-Champaign in 1976 under the supervision of Professor David. Y. Curtin and Professor Iain C. Paul.

2. My research interests include the analysis of chemical compounds using solid state characterization analytical techniques and instrumentation, such as single crystal X-ray diffraction, powder X-ray diffraction, thermal gravimetric analysis, differential scanning calorimetry, and hot stage microscopy.

3. I am an established expert on polymorphism, crystal engineering and X-ray crystallography. I have published over 300 papers. I am a well known author and have published books such as "Crystal Engineering - The Design of Organic Solids" published in 1989. I am co-author of "The Weak Hydrogen Bond in Structural Chemistry and Biology" (Oxford University Press, ISBN-13: 978-0-19-850970-7) first published in 1999. I was a co-editor of Acta Crystallographica between 1994 and 2008, a journal reporting fundamental advances in all areas of crystallography including experimental and theoretical studies of the

properties and arrangements of atoms, ions and molecules in the solid state, and the theoretical and experimental aspects of the various methods to determine these arrangements. I am also a member of the Editorial Advisory Boards of Crystal Growth & Design and CrystEngComm, journals that publish articles on the physical, chemical, and biological phenomena and processes related to crystal engineering, crystal growth and design of new materials. I am a consulting editor of Accounts of Chemical Research, one of the most prestigious journals published by the American Chemical Society. I am on the International Editorial Advisory Board of Angewandte Chemie which is one of the foremost chemistry journals today. Additional information on my research interests, publications, awards, and honours can be obtained from my website, http://202.41.85.161/~grd/ and in http://en.wikipedia.org/wiki/Gautam_Radhakrishna_Desiraju which is my Wikipedia entry.

4. I have reviewed the patent application in this case, U.S. Application No. 10/802,627, and I also reviewed the following supporting materials: U.S. Patent No. 5,399,578 to Bühlmayer et al. ('578); PCT Publication No. WO 02/06253 to Marti et al. ('253); the Declarations of Dr. Tamas Koltai and Dr. Valerie Niddam-Hildesheim filed July 23, 2008 in this case; and the Office Action issued by Examiner Susannah Lee Chung on November 7, 2008.

5. The '578 patent describes the isolation of valsartan in example 16 "from ethyl acetate." The '578 patent fails to state whether the product of example 16 crystalline or amorphous. The melting range provided for the product of Example 16 is 105-115°C.

6. The '253 publication, which includes Bühlmayer as an inventor, reports that valsartan as described in EP 0443983 (which counsel tells me is a counterpart to the '578 patent) has a melting enthalpy of 12 kJ/mol ('253, pages 1-2).[1]

7. In my professional judgment, this degree of melting enthalpy indicates a substantial amount of order (crystallinity) in the material isolated in the '578 patent from ethyl acetate.

[1] I read the '253 publication to mean that the "free acid valsartan" described at the bottom of page 1, melting in a closed crucible at 80-95°C and having a melting enthalpy of 12 kJ/mol, is the valsartan obtained from EP 0443983.

8. The '578 patent also describes the isolation of valsartan in Example 37, with a melting point to 116-117° C. I agree with the conclusion of Dr. Koltai that this is a sharp melting point that indicates a highly crystalline material. In my professional judgment, a highly crystalline material is expected to have a melting enthalpy substantially higher than 1 J/g.

9. I reviewed the declaration of Dr. Koltai, who described the preparation of valsartan isolated from ethyl acetate in the Declaration Dr. Niddam-Hildesheim, by the same method as described in example 16 of the '578 patent. Dr. Koltai acquired PXRD diffractograms for two samples of Dr. Niddam-Hildesheim's material, and found them to be essentially identical. *I agree with the conclusions of Dr. Koltai that the PXRD diffractogram of valsartan prepared according to Example 16 of the '578 patent is substantially different from the PXRD diffractogram of amorphous material isolated in the instant application (Fig. 2).* It is clear that Fig. 2 of the present application is smooth halo with no significant relief. By contrast, the valsartan prepared according to example 16 of the '578 patent has peaks which indicate that a fair amount of crystallinity is present.

10. I reviewed the office action of Examiner Chung dated November 7, 2008. I disagree with the assertion in the office action, stating that "the amorphous form [of valsartan] was in the prior art." The prior art '578 patent provides valsartan with a melting enthalpy of 12 kJ/mol, and a PXRD diffractogram (in the Koltai declaration) indicating a substantial amount of order in the material. A sample with a substantial amount of order is at best, an impure amorphous material.

11. In my opinion, the essentially flat DSC trace (Fig. 3 of the instant invention) indicates essentially no measurable melting enthalpy in the range of 80-140°C.

12. In my opinion therefore, the peaks in the PXRD of the valsartan prepared according to example 16 of the '578 patent (as discussed in the Koltai declaration) confirm that valsartan crystallized from ethyl acetate would have a substantial melting enthalpy, such as 12 kJ/mol reported in the '253 publication. This melting enthalpy would certainly be substantially larger than 1 J/g.

13. Additionally, I agree with the conclusion of the Koltai declaration that 12 kJ/mol is equivalent to about 28 J/g in this case, because of the molecular weight of valsartan. Therefore, the valsartan discussed in the '253 publication has more than a 28-fold higher melting enthalpy than the presently claimed valsartan. Thus, the valsartan discussed in the '253 publication has a substantially larger melting enthalpy than in the current claims. As noted above in my paragraph 11, there is no detectable melting enthalpy at all in Fig. 3, the DSC of pure amorphous valsartan in the present application.

14. Impure amorphous materials, such as that obtained in the '578 patent, are undesirable pharmaceutical materials. A highly impure amorphous material lacks the advantages of a pure amorphous material, such as greater solubility, bioavailability, stability, and ease of handling. The impurity here refers to crystallographic impurity rather than chemical impurity. The sample is crystallographically impure because it has a partly crystalline and a partly amorphous character. A material that has partial amorphous and partial crystalline character is generally less suitable as a drug, because the mixed parameters result in inconsistent physical behaviour of the material, for example, uneven and variable dissolution characteristics.

15. Furthermore, in my professional opinion, the preparation of a pure amorphous material is not predictable. Conventional techniques such as spray-drying, chromatography, and precipitation in solvent systems are not *a priori* dependable methods to prepare a pure amorphous or polymorphic material absent considerable experimentation. General methods of routinely preparing amorphous forms of solid drugs are not in existence at the present time.

16. The undersigned declares that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the life so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Gautam R. Desiraju

19 February 2009

Professor Gautam R. Desiraju, Ph.D
University of Hyderabad, India

Date